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A61K 31/423 (2006.01)

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(21) International Application Number:

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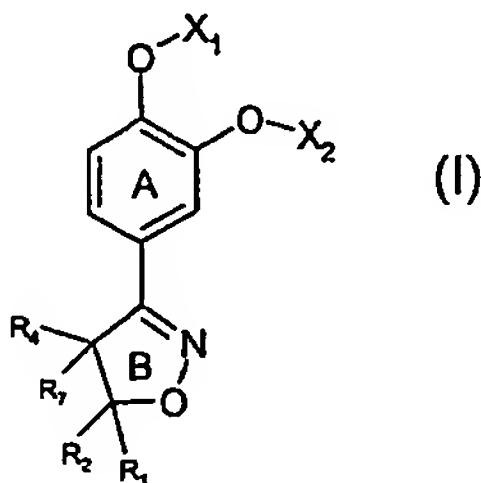
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19 October 2006

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: CONDENSED ISOXALINE DERIVATIVES AS INHIBITORS OF PHOSPHODIESTERASE TYPE-IV



(57) Abstract: The present invention relates to isoxazoline derivatives of formula (I), which can be used as selective inhibitors of phosphodiesterase (PDE) type IV. In particular, compounds disclosed herein can be useful in the treatment of AIDS, asthma, arthritis, bronchitis, chronic obstructive pulmonary disease (COPD), psoriasis, allergic rhinitis, shock, atopic dermatitis, Crohn's disease, adult respiratory distress syndrome (ARDS), eosinophilic granuloma, allergic conjunctivitis, osteoarthritis, ulcerative colitis and other inflammatory diseases in a patient, particularly in humans. The present invention also relates to processes for the preparation of disclosed compounds, as well as pharmaceutical compositions thereof, and their use as phosphodiesterase (PDE) type IV inhibitors.

WO 2006/085212 A3

## INTERNATIONAL SEARCH REPORT

PCT/IB2006/000285

## A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D498/10 C07D261/20 C07D498/04 A61K31/423 A61K31/424  
 A61P11/00 A61P31/18

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data, BEILSTEIN Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|--|-----------------------|
|-----------|--|-----------------------|

P, X

WO 2005/021515 A (RANBAXY LABORATORIES  
 LIMITED; PALLE, VENKATA, P; BALACHANDRAN,  
 SARALA;) 10 March 2005 (2005-03-10)  
 claim 1  
 page 39 - page 45  
 page 47 - page 50  
 examples

1-29

-/-

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

## \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*&\* document member of the same patent family

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28/08/2006

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Authorized officer

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| INTERNATIONAL SEARCH REPORT                          |  |                       |
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|  |  | PCT/IB2006/000285     |
| C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT |  |                       |
| Category*  | Citation of document, with indication, where appropriate, of the relevant passages   | Relevant to claim No. |
| P,X  | <p>DATABASE CA [Online]<br/>           CHEMICAL ABSTRACTS SERVICE, COLUMBUS,<br/>           OHIO, US;<br/>           DAS, BISWANATH ET AL: "Synthetic studies<br/>           on natural products. Part 20. Synthesis of<br/>           novel spiro-2-isoxazoles derived from<br/>           parthenin"<br/>           XP002380558<br/>           retrieved from STN<br/>           Database accession no. 2005:1160450<br/>           compounds with RN 882164-94-5,<br/>           882164-95-6, 882164-99-0, 882165-00-6<br/>           abstract<br/>           &amp; INDIAN JOURNAL OF CHEMISTRY, SECTION B:<br/>           ORGANIC CHEMISTRY INCLUDING MEDICINAL<br/>           CHEMISTRY , 44B(10), 2149-2151 CODEN:<br/>           IJSBDB; ISSN: 0376-4699, 2005,</p> | 1,3                   |
| X  | <p>WO 95/14680 A (PFIZER INC; KLEINMAN,<br/>           EDWARD, F) 1 June 1995 (1995-06-01)<br/>           claims<br/>           page 21; example 27</p>  | 1-29                  |
| X  | <p>FIHI R ET AL: "REACTION SES METHYLENE<br/>           GAMMA-BUTYROLACTONES AVEC LES<br/>           ARYLNITRILOXYDES. EVOLUTION INATTENDUE DU<br/>           BISADDUIT ISSU DE LA<br/>           5-METHYLENE(5H)FURAN-2-ONE"<br/>           BULLETIN DES SOCIETES CHIMIQUES BELGES,<br/>           vol. 104, no. 1, 1995, pages 55-62,<br/>           XP009044216<br/>           ISSN: 0037-9646<br/>           compound 6F</p>   | 1,3                   |
| X  | <p>WO 95/14681 A (PFIZER INC; KLEINMAN,<br/>           EDWARD, F) 1 June 1995 (1995-06-01)<br/>           page 13; example 16<br/>           page 21; compound 21</p>  | 1-29                  |
| X  | <p>FOS, EMPAR ET AL: "Synthesis of isomeric<br/>           series of aryltetrahydrobenzoxazoles and<br/>           arylcyclopentisoxazoles"<br/>           JOURNAL OF HETEROCYCLIC CHEMISTRY , 29(1),<br/>           203-8 CODEN: JHTCAD; ISSN: 0022-152X,<br/>           1992, XP002393576<br/>           compounds 3C, 4C</p>  | 1,3                   |
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| C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT |   |                       |
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| Category*  | Citation of document, with indication, where appropriate, of the relevant passages  | Relevant to claim No. |
| X  | <p>DATABASE CAPLUS [Online]<br/>CHEMICAL ABSTRACTS SERVICE, COLUMBUS,<br/>OHIO, US;<br/>KONOPIKOVA, M. ET AL: "1,3-Dipolar<br/>cycloadditions of heterocycles. XXIII.<br/>Cycloadditions of benzonitrile oxides to<br/>N-(2,6-dialkylphenyl)maleimides"<br/>XP002393583<br/>retrieved from STN<br/>Database accession no. 1992:151622<br/>compounds with RN 139395-56-5,<br/>139395-65-6, 139395-74-4, 139395-77-0,<br/>139395-67-1, 139395-70-6<br/>abstract<br/>&amp; CHEMICAL PAPERS , 45(6), 789-805 CODEN:<br/>CHPAEG; ISSN: 0366-6352, 1991,</p>                    | 1,3                   |
| X  | <p>DATABASE CAPLUS [Online]<br/>CHEMICAL ABSTRACTS SERVICE, COLUMBUS,<br/>OHIO, US;<br/>BRAHMESHWARI, G. ET AL: "Synthesis and<br/>biological activity of fused heterocycles<br/>derived from embelin"<br/>XP002393584<br/>retrieved from STN<br/>Database accession no. 1991:228802<br/>compounds with RN 133701-91-4,<br/>133701-95-8, 133701-87-8<br/>abstract<br/>&amp; INDIAN JOURNAL OF CHEMISTRY, SECTION B:<br/>ORGANIC CHEMISTRY INCLUDING MEDICINAL<br/>CHEMISTRY , 30B(3), 369-70 CODEN: IJSBDB;<br/>ISSN: 0376-4699, 1991,</p>                                | 1,3                   |
| X  | <p>DATABASE CAPLUS [Online]<br/>CHEMICAL ABSTRACTS SERVICE, COLUMBUS,<br/>OHIO, US;<br/>KUMAR, K. AJAY ET AL: "Synthesis of<br/>3-aryl-5N-aryl-4,6-dioxo-pyrrolo[3,4-d]-7,<br/>8- dihydroisoxazoles via 1,3-dipolar<br/>cycloaddition reaction"<br/>XP002393585<br/>retrieved from STN<br/>Database accession no. 2001:302770<br/>compounds with RN 348630-00-2 to<br/>348630-06-8<br/>abstract<br/>&amp; INDIAN JOURNAL OF CHEMISTRY, SECTION B:<br/>ORGANIC CHEMISTRY INCLUDING MEDICINAL<br/>CHEMISTRY , 40B(4), 269-273 CODEN: IJSBDB;<br/>ISSN: 0376-4699, 2001,</p> | 1,3                   |
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| C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT |  |                       |
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| Category*  | Citation of document, with indication, where appropriate, of the relevant passages   | Relevant to claim No. |
| X  | <p>DATABASE CAPLUS [Online]<br/>CHEMICAL ABSTRACTS SERVICE, COLUMBUS,<br/>OHIO, US;<br/>SINGAL, K. K. ET AL: "1,3-Dipolar<br/>cycloaddition reactions of nitrile oxides<br/>with N-arylmaleimides leading to the<br/>synthesis of 3,5-diaryl-3a,4,6,6a-<br/>tetrahydro-4H,6H-pyrrolo[3,4-d]isoxazole-4<br/>,6-diones"<br/>XP002393586<br/>retrieved from STN<br/>Database accession no. 2001:82529<br/>compounds with RN 333404-83-4,<br/>333404-89-0, 333404-93-6, 333405-03-1,<br/>333404-97-0, 333405-03-1, 333405-08-6,<br/>333405-13-3<br/>abstract<br/>&amp; CHEMICAL &amp; ENVIRONMENTAL RESEARCH , 9(1<br/>&amp; 2), 47-53 CODEN: CEREEH; ISSN:<br/>0971-2151, 2000,</p> | 1,3                   |
| X  | <p>DATABASE CAPLUS [Online]<br/>CHEMICAL ABSTRACTS SERVICE, COLUMBUS,<br/>OHIO, US;<br/>BRAHMESHWARI, G. ET AL: "Synthesis of<br/>3-arylnaphth[2,3-d]isoxazole-4,9-diones<br/>from Lawsone"<br/>XP002393587<br/>retrieved from STN<br/>Database accession no. 1995:333432<br/>compounds with RN 161497-83-2, 161497-88-7<br/>abstract<br/>&amp; INDIAN JOURNAL OF CHEMISTRY, SECTION B:<br/>ORGANIC CHEMISTRY INCLUDING MEDICINAL<br/>CHEMISTRY , 34B(2), 139-40 CODEN: IJSBDB;<br/>ISSN: 0376-4699, 1995,</p>   | 1,3                   |
| X  | <p>DATABASE CAPLUS [Online]<br/>CHEMICAL ABSTRACTS SERVICE, COLUMBUS,<br/>OHIO, US;<br/>HUANG, HAI-HONG ET AL: "Synthesis of<br/>chiral<br/>5-1-menthyloxybutyrolacto[3,4-d]isoxazolin<br/>e derivatives"<br/>XP002393588<br/>retrieved from STN<br/>Database accession no. 2003:951601<br/>compounds with RN 476683-28-0, 561317-49-5<br/>abstract<br/>&amp; GAODENG XUEXIAO HUAXUE XUEBAO , 24(11),<br/>2000-2004 CODEN: KTHPDM; ISSN: 0251-0790,<br/>2003,</p>  | 1,3                   |



## INTERNATIONAL SEARCH REPORT

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages  | Relevant to claim No. |
|-----------|---|-----------------------|
| X         | GB 2 284 600 A (* SHELL INTERNATIONALE RESEARCH MAATSCHAPPIJ B.V)<br>14 June 1995 (1995-06-14)<br>claim 11<br>example 17; table 1<br>-----  | 1,3                   |
| X         | SUBRAMANIAN T ET AL: "FACILE SYNTHESIS OF 3-AROYL-3-SULFOLENES THROUGH CYCLOADDITIONS OF ARYLNITRILE OXIDES & 3-SULFOLENE"<br>SYNTHETIC COMMUNICATIONS, MARCEL DEKKER, INC., BASEL, CH,<br>vol. 27, no. 15, 1997, pages 2557-2562, XP009041534<br>ISSN: 0039-7911<br>compounds 3D,3F<br>-----   | 1,3                   |
| X         | GABOURY J A ET AL: "Enantiocontrolled synthesis of burseran, brassilignan, dehydroxycubebin, and other tetrahydrofuran lignans in both enantiomeric forms. Application of intermolecular nitrile oxide cycloadditions and lipase-mediated kinetic resolutions"<br>JOURNAL OF ORGANIC CHEMISTRY, AMERICAN CHEMICAL SOCIETY. EASTON, US,<br>vol. 58, no. 8, 1993, pages 2173-2180, XP002330566<br>ISSN: 0022-3263<br>compounds 9C,9D<br>----- | 1,3                   |
| X         | HASSIKOU A ET AL: "Synthèse de nouveaux polyhétérocycles"<br>TETRAHEDRON LETTERS, ELSEVIER, AMSTERDAM, NL,<br>vol. 42, no. 34,<br>20 August 2001 (2001-08-20), pages 5857-5861, XP004295942<br>ISSN: 0040-4039<br>compound 16<br>-----  | 1,3                   |
| X         | SYASSI B ET AL: "Addition Dipolaire-1,3 des Arylnitriloxydes avec quelques Dipolarophiles Olefiniques sur Alumine en Milieu sec et sous Micro-ondes"<br>TETRAHEDRON LETTERS, ELSEVIER, AMSTERDAM, NL,<br>vol. 38, no. 51,<br>22 December 1997 (1997-12-22), pages 8855-8858, XP004162383<br>ISSN: 0040-4039<br>compound 7H<br>-----   | 1,3                   |
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| INTERNATIONAL SEARCH REPORT                          |   | PCT/IB2006/000285     |
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| C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT |   |                       |
| Category*  | Citation of document, with indication, where appropriate, of the relevant passages  | Relevant to claim No. |
| X  | SYASSI B ET AL: "Short communication"<br>TETRAHEDRON LETTERS, ELSEVIER, AMSTERDAM,<br>NL,<br>vol. 40, no. 40,<br>1 October 1999 (1999-10-01), pages<br>7205-7209, XP004179018<br>ISSN: 0040-4039<br>compounds 4E,5E<br><br>-----  | 1,3                   |
| X  | SIBI M P ET AL: "SYNTHESIS OF LIGNAN<br>NATURAL PRODUCTS (PLUS OR<br>MINUS)DEHYDROXYCUBEBIN AND (PLUS OR<br>MINUS)BURSERAN BY INTERMOLECULAR NITRILE<br>OXIDE CYCLOADDITION"<br>SYNLETT, THIEME INTERNATIONAL, STUTTGART,<br>DE, no. 1, January 1992 (1992-01), pages<br>83-84, XP001204506<br>ISSN: 0936-5214<br>compound 3<br><br>----- | 1,3                   |
| X  | SALGADO-ZAMORA H ET AL: "OXIDATIVE<br>DEGRADATION OF ARYLFURO-1,2-OXAZOLES TO<br>ARYLNITRILES BY POTASSIUM PERMANGANATE"<br>HETEROCYCLIC COMMUNICATIONS, FREUND<br>PUBLISHING HOUSE, TEL AVIV, IL,<br>vol. 7, no. 3, 2001, pages 209-212,<br>XP009041526<br>ISSN: 0793-0283<br>compound 3A<br><br>-----                                   | 1,3                   |
| X  | TIAN L ET AL: "1,3-Dipolar cycloaddition<br>reactions of nitrile oxides to<br>prop-1-ene-1,3-sultone"<br>JOURNAL OF HETEROCYCLIC CHEMISTRY,<br>HETEROCORPORATION. PROVO, US,<br>vol. 40, no. 6, 2003, pages 1071-1074,<br>XP002330565<br>ISSN: 0022-152X<br>compound 4L<br><br>-----  | 1,3                   |

# INTERNATIONAL SEARCH REPORT

PCT/IB2006/000285

## Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claims 4 and 5 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☒ No protest accompanied the payment of additional search fees.



International Application No. PCT/IB2006 /000285

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-5(part); 6-13;14(part); 15,19-29

Compounds of claim 1 in which R1 and R2 together form a ring (i. e. spirocondensed compounds), processes for their preparation (and for intermediates) and their use as PDE-IV inhibitors

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2. claims: 1-5(part); 14(part), 17,18

Compounds of claim 1 in which R2 and R4 together form a ring (i. e. orthocondensed compounds), processes for their preparation and their use as PDE-IV inhibitors

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# INTERNATIONAL SEARCH REPORT

PCT/IB2006/000285

| Patent document<br>cited in search report | Publication<br>date | Patent family<br>member(s)   | Publication<br>date  |
|---|---------------------|--|--|
| WO 2005021515 A                           | 10-03-2005          | AU 2004268847 A1<br>CA 2537185 A1<br>EP 1663999 A2   | 10-03-2005<br>10-03-2005<br>07-06-2006   |
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| WO 9514681 A                              | 01-06-1995          | AT 154932 T<br>AU 687452 B2<br>AU 7821894 A<br>BR 9408174 A<br>CA 2176255 A1<br>CN 1136314 A<br>CZ 9601510 A3<br>DE 69404044 D1<br>DE 69404044 T2<br>DK 730588 T3<br>EG 20693 A<br>EP 0730588 A1<br>ES 2104424 T3<br>FI 945557 A<br>GR 3024133 T3<br>HU 76784 A2<br>IL 111670 A<br>JP 2802547 B2<br>JP 9500147 T<br>KR 182324 B1<br>NO 962127 A<br>NZ 274244 A<br>PL 314605 A1<br>US 5716967 A | 15-07-1997<br>26-02-1998<br>13-06-1995<br>27-05-1997<br>01-06-1995<br>20-11-1996<br>15-01-1997<br>07-08-1997<br>16-10-1997<br>08-12-1997<br>30-11-1999<br>11-09-1996<br>01-10-1997<br>27-05-1995<br>31-10-1997<br>28-11-1997<br>16-08-1998<br>24-09-1998<br>07-01-1997<br>01-05-1999<br>24-05-1996<br>22-09-1997<br>16-09-1996<br>10-02-1998 |
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